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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,785	10/03/2005	Marco Cattaruzza	DEBE:053US	1068

32425 7590 05/31/2007
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
05/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,785	CATTARUZZA ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 4/13/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/14/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 4/13/07, claims 1-10 are pending in the application. Claims 4-10 remain withdrawn. Claims 1-3 are currently under examination.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections—withdrawn

The objection to Claims 1–3 for reciting non-elected subject matter is withdrawn in view of Applicants' amendments to the claims.

Sequences—notice to comply

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures..

In reply to the previous Action, stating that the nucleic acid sequence set forth in Fig. 1 does not have a SEQ ID NO: identifier as currently required by 37 CFR § 1.821, Applicants have stated that a new sequence listing has been provided along with the amendment to Fig. 1 to add "SEQ ID NO:64."

However, neither a paper copy nor a CRF for the sequence listing referred to is found in the electronic IFW or in the Supplemental Complex Repository for Examiners (SCORE).

Thus, SEQ ID NO:64 is not listed in the current sequence listing now on file with the Office.

Correction is required to bring the application into sequence compliance.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Claim Rejections - 35 USC § 102—new

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (1995) *J. Biol. Chem.* 270:15320-15326.

While the previous Action had indicated that decoy oligonucleotides comprising SEQ ID NO:17 were free of the prior art searched, upon further consideration, claims 1 and 2 are broader than previously realized. Broadest reasonable interpretation of Claim 1 includes recombinant plasmid DNA (i.e., an isolated double stranded DNA) containing the eNOS promoter sequence, which, in turn, comprises instant SEQ ID NO:17.

This is interpretation is reasonable in view of 1) the open-ended transition phrase "comprising" and 2) the definition of decoy oligonucleotides given at paragraph 16 of the instant application publication, which states that "The terms "decoy oligonucleotide" or "cis-element decoy" used in the present document refer to a double-strand DNA molecule, which provides a sequence, which corresponds to or is similar to the natural core-binding sequence of a DNA-binding protein or protein complex in the genome..."

The Examiner notes the definition at paragraph 34 of the instant application publication, which states that "the cis-element decoy according to the invention should not exceed a given length, because this is limiting for the transport into the target cell," however, the length is not explicitly defined in the claims, the lengths given at paragraph 34 are exemplary in nature only, and these limitations may not be imported into the claim (MPEP 2111.01, Section II).

Zhang et al. taught plasmid constructs containing the human eNOS gene promoter (Fig. 1 and 2). The plasmids were transfected into cells to characterize the activity of the eNOS promoter. Both full and truncated versions of the promoter were cloned and transfected. The eNOS promoter sequence cloned comprises instant SEQ ID NO:17, and thereby SEQ ID NO:18 (see Fig. 1, line –820).

Thus, Zhang et al. taught a decoy oligonucleotide comprising SEQ ID NO:17 according to the definitions set forth in the instant application. Absent evidence to the contrary the plasmid formulations used by Zhang et al. would be pharmaceutically acceptable within the guidelines of the instant application, which provides no explicit definition of formulations specifically included or excluded by the claims.

Amending instant claim 1 to restrict the claimed decoy to a specific length not taught by Zhang et al. would be useful in overcoming the instant rejection.

Claim Rejections - 35 USC § 112, first paragraph—maintained

Claim 3 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating coronary heart disease and rheumatoid arthritis comprising administering an oligonucleotide decoy comprising SEQ ID NO:17, does not reasonably provide enablement for methods of inhibiting coronary heart disease or rheumatoid arthritis or any of the several other diseases now recited in claim 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

With the amendment of 4/13/07, Claim 3 is drawn to a method for the inhibition of several different diseases, as recited in claim 3, including bacterial infections, herpes, and human immunodeficiency viruses, multiple sclerosis, and diabetes, comprising administering a decoy oligonucleotide comprising SEQ ID NO:17.

Adequate support does not exist in the instant application enabling one of ordinary skill in the art to use the instantly claimed double-stranded decoy oligonucleotide to inhibit every disease listed in claim 3 without undue experimentation.

At issue here is the lack of evidence establishing an association between the $^{-786}$C/T SNP genotype in eNOS with each of the diseases now recited in claim 3. While post-filing art shows a connection between the $^{-786}$C/T SNP and an increased risk of coronary heart disease and rheumatoid arthritis (Cattaruzza et al., 2004, *Circ. Res.* 95:841-847; Melchers et al., 2006, *Arthritis & Rheumatism* 54:3144-3151), there is no evidence linking the $^{-786}$C/T SNP with any of the many other diseases listed in claim 3. For example, there are no representative examples either in the specification or the prior or post-filing art to suggest that the eNOS ^{786}C/T SNP polymorphism is specifically linked to multiple sclerosis, diabetes, or graft-versus-host disease, or that the administration of SEQ ID NO:17 or any other decoy designed to counteract this SNP may be used to inhibit or treat all other diseases now listed. While the polymorphism may be

present in other diseases, evidence that the correction of this polymorphism would inhibit or treat the disease has not been established in every case. The diseases listed are extremely diverse ranging from cardiovascular to neurodegenerative, and are multi-factorial in nature.

Consequently, while the post-filing art provides evidence suggesting that the administration of decoys directed to eNOS transcription factors may be used to alleviate the symptoms associated with CHD and RA due to the ^{786}C/T SNP, there is insufficient guidance and evidence in the prior art and specification to enable one of skill to treat the many other diseases now listed. As a result one of skill would be left to *de novo* experimentation to develop the methods commensurate in scope with the claims necessary to use the instant oligonucleotides to treat each of the diseases intended. Such experimentation is considered to be undue.

Adequate enabling disclosure must be present at the time of filing. MPEP 2164.01(b) states in part that "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112 is satisfied. MPEP 2164.01(c) states in part that "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)." While claim 3 is drawn to a method, the method uses compounds comprising instant SEQ ID NO:5 to inhibit a wide variety of specific diseases.

While the specification and prior art disclose examples of using decoy oligonucleotides to correct for the ^{786}C/T SNP and thereby treat symptoms associated with vascular disease and

arthritis, these examples do not bear a reasonable correlation with the full scope of protection now sought for inhibiting the many other diseases now listed in claim 3.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Replacing the word "inhibition" with "treating" and amending claim 3 to recite those diseases for which enabling disclosure was present at the time of filing and/or for which the post-filing art substantiates the association, such as coronary heart disease and rheumatoid arthritis, would be remedial.

Response to Arguments

Applicant's arguments submitted 4/13/07 with respect to the previous rejection of claims 2 and 3 under this section have been fully considered and are persuasive in part.

The claims are drawn to a specific oligonucleotide sequence, SEQ ID NO:17. To reject the claim for lack of enablement, the Examiner must provide evidence or technical reasoning to show that one of skill in the art could not use the claimed invention, the instant decoy, SEQ ID NO:5 in the manner required by the claim. In the instant case, while the art indicates that challenges and difficulties remain with regard to the delivery of single and double stranded nucleic acids in general, the Examiner is unable to find any evidence that one of skill would be unable to deliver to cells *in vivo* the specific oligonucleotide now recited—SEQ ID NO:17.

Therefore, the instant rejection has been modified. While the claims are enabled for the delivery of SEQ ID NO:17, enabling disclosure is not found for using the instant sequence to inhibit and/or treat each of the diseases now listed.

Furthermore, the Declaration submitted under 37 CFR 1.132 filed 4/13/07 has been considered. Evidence referred to therein (which were not submitted with the original response but were subsequently supplied by fax and are attached herewith) shows the uptake and delivery of double stranded decoys into bronchial epithelium in mice when administered intranasally and into psoriatic skin when administered topically. Thus, the Declaration is sufficient to overcome the previous rejection under this section with regard to the issue of *in vivo* delivery. The Declaration, however, does not address issues concerning the nexus between the eNOS ^{786}C/T SNP, SEQ ID NO:17, and the many diseases now recited, and is therefore not remedial to this portion of the rejection, as explained above.

In their remarks traversing the rejection, Applicants refer to attached post-filing articles published by Cattaruzza et al. and Melchers et al. Although, not found in the response itself, the Examiner notes the articles in the rejection above. These are considered to be sufficient evidence of the nexus between the ^{786}C/T SNP and the administration of decoys to treat CHD and RA. Therefore, the claims are considered to be enabling for the treatment of these diseases by the administration of SEQ ID NO:17.

Response to Applicants' Arguments

Applicants' arguments presented on 4/13/07 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
May 23, 2007
Examiner, Art Unit 1635

/Sean McGarry/
Primary Examiner AU 1635

Notice to Comply	Application No.	Applicant(s)	
	10527785	CATTARUZZA ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Applicants' amendent adding SEQ ID NO:64 to the specification is not reflected by the current sequence listing. While Applicants state a new sequence listing has been filed, no such listing is found in IFW. SEQ ID NO:64 does not appear in the sequence listing now on file.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification**.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
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